Altered proliferation and networks in neural cells derived from idiopathic autistic individuals.

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Public Summary:
This publication reports a model of idiopathic autism using reprogrammed cells from autistic individuals with enlarged brains. Our genome sequencing data showed that some of these patients carry genetic mutation related to cell cycle. In fact, we do detect a fast proliferation on the neural progenitor cells that might explain the big brain phenotype in this subgroup. Moreover, neurons derived from the iPSC have clear altered synaptogenesis leading to defects in network synchronization. Our gene expression analyses pointed to misregulated pathways in neurotransmitters that could be potential therapeutic targets. Finally, we use the system to study the drug response from these networks. IGF-1, a candidate drug current in clinical trials for autism, showed promising network rescue capacity. We also observed a differential individual response to IGF-1, suggesting that our platform could be used to stratify the autistic population for clinical trials.

Scientific Abstract:
Autism spectrum disorders (ASD) are common, complex and heterogeneous neurodevelopmental disorders. Cellular and molecular mechanisms responsible for ASD pathogenesis have been proposed based on genetic studies, brain pathology and imaging, but a major impediment to testing ASD hypotheses is the lack of human cell models. Here, we reprogrammed fibroblasts to generate induced pluripotent stem cells, neural progenitor cells (NPCs) and neurons from ASD individuals with early brain overgrowth and non-ASD controls with normal brain size. ASD-derived NPCs display increased cell proliferation because of dysregulation of a beta-catenin/BRN2 transcriptional cascade. ASD-derived neurons display abnormal neurogenesis and reduced synaptogenesis leading to functional defects in neuronal networks. Interestingly, defects in neuronal networks could be rescued by insulin growth factor 1 (IGF-1), a drug that is currently in clinical trials for ASD. This work demonstrates that selection of ASD subjects based on endophenotypes unraveled biologically relevant pathway disruption and revealed a potential cellular mechanism for the therapeutic effect of IGF-1.Molecular Psychiatry advance online publication, 5 July 2016; doi:10.1038/mp.2016.95.